is used as a therapeutic composition in humans, one skilled in the art would recognize that said uricase is free of large aggregates." Office Action, page 2. Further, the Office Action asserts that the Patent Office is not equipped to conduct comparisons of instant products with prior art and the burden is on the applicant to establish a patentable distinction between the claimed and referenced uricase. Claim 33 is rejected because the patentability of a product does not depend on the method used in producing the product.

Applicants respectfully traverse this rejection on the grounds that the R&D Focus reference satisfies neither the criteria for anticipation under 35 U.S.C. §102(b) nor the criteria for an enabling disclosure required for a prior art reference relied upon to make a statutory rejection.

To anticipate a claim under 35 U.S.C. §102(b), a reference must teach each and every element of the claim, such that the invention must be shown in as complete detail as is contained in the claim. MPEP § 2131. Here, Claims 2-8, 17-28, and 33 all depend directly or indirectly from Claim 1, which recites "[p]urified urate oxidase (uricase) substantially free of aggregates larger than octamers." The R&D Focus reference does not explicitly or inherently teach purified urate oxidase (uricase) substantially free of aggregates larger than octamers, and thus does not anticipate Claim 1. Likewise, the R&D Focus reference does not teach the additional claim limitations found in Claims 2-8, 17-28, and 33. Because the R&D Focus reference does not teach each and every element as set forth in the claim, this reference does not anticipate the rejected claims under 35 U.S.C. §102(b) and the rejection should be withdrawn.

Not only does the R&D Focus reference not anticipate the rejected claims, it is not even suitable as a prior art reference for purposes of statutory rejection. In order to make a *prima facie* case for rejection, a prior art reference must be operable, that is, it must contain an enabling disclosure such that "one of ordinary skill in the art could have combined the publication's description with his [or her] own knowledge to make the claimed invention." MPEP §2121.01, citing *In re Donohue*, 766 F.2d at 531, 226 USPQ 619. In the present case, the Office Action asserts that "[b]ecause the reference uricase is used as a therapeutic composition in humans, one skilled in the art would recognize that said uricase is free of large aggregates." Applicants point out that the R&D Focus reference merely discloses a licensing agreement concerning a PEGylated form of recombinant uricase that will be developed for treatment of gout. Applicants respectfully disagree that one of skill in the art would, upon reading this disclosure of a license

agreement concerning plans for future development of a PEGylated form of recombinant uricase, recognize that said uricase is free of large aggregates. First, as discussed above, the R&D Focus reference does not teach that the reference uricase is free of large aggregates. Second, the Office Action has not provided any basis for asserting it was known in the art that only uricase that is free of large aggregates would be used as a therapeutic composition in humans. In fact, the above-captioned application teaches that purified preparations of naturally occurring and recombinant uricases usually contain a mixture of very large aggregates of the enzyme (page 11, lines 22-23), and that large aggregates were likely present in enzyme preparations used for previous syntheses of PEGylated uricase (page 11, line 31 to page 12, line 1).

Finally, the Office Action notes that "[t]he specification teaches that the unfractionated PKS of SEQ ID NO: 3 of the instant invention was obtained from Bio-Technology General Limited (page 16, line 21)" and "[t]he burden is on the applicant to establish a patentable distinction between the claimed and referenced uricase." Office Action, page 2. Applicants will proceed to distinguish between the unfractionated PKS uricase received from Bio-Technology General Limited and the claimed "[p]urified urate oxidase (uricase) substantially free of aggregates larger than octamers." First, the unfractionated PKS uricase from Bio-Technology General Limited (page 16, lines 21-22) had not been treated by the method disclosed in the above-captioned application to generate the claimed "[p]urified urate oxidase (uricase) substantially free of aggregates larger than octamers." Second, the R&D Focus reference discloses only a PEGylated form of recombinant uricase (emphasis added) while the "[u]nfractionated PKS uricase" obtained from Bio-Technology General Limited disclosed at page 16, line 21 was not PEGylated, as the next two lines of the specification disclose that unfractionated PKS uricase was "coupled to 10-kDa PEG using the *p*-nitrophenyl carbonate derivative of PEG (NPC-PEG) . . ." (page 16, lines 22-23). Third, the R&D Focus reference does not teach whether the uricase disclosed on August 24, 1998, was a native uricase or a chimeric uricase, nor does the reference teach the species of origin of the uricase, nor does the reference teach the amino acid sequence of the uricase. In contrast, the polypeptide having SEQ ID NO: 3 is a chimeric uricase of porcine origin having two mutations, in which arginine 291 has been replaced by lysine (R291K) and threonine 301 has been replaced by serine (T301S),

referred to as the "PKS uricase" (page 8, lines 22-24). In summary, the reference does not disclose the the claimed uricases and the rejection cannot stand.

Regarding the rejection of Claim 33 on grounds that the patentability of a product does not depend on the method used in producing the product, Applicants point out that Claim 33 is directed to an isolated uricase prepared by the method of Claim 29, a method that separates uricase aggregates larger than octamers and excludes such aggregates from the purified uricase. The R&D Focus reference does not teach an isolated uricase substantially free of aggregates larger than octamers. Thus, the R&D Focus reference does not anticipate Claim 33 and the rejection should be withdrawn.

Trademark Registration for Puricase®

Claims 1-8, 17-28, and 33 are rejected under 35 U.S.C. §102(b) as being anticipated by the trademark registration for Puricase® Registration No. 2,246,623. According to the Office Action, Puricase® (Registration No. 2,246,623) teaches a PEG-uricase. The Office Action further asserts that, "[b]ecause the referenced uricase is used as a pharmaceutical composition in humans, one skilled in the art would recognize that said uricase is free of large aggregates." Office Action, page 3. The Office Action further states that the Patent Office is not equipped to compare instant products with prior art and "[t]he burden is on the applicant to establish a patentable distinction between the claimed and reference uricase." Office Action, page 3. Claim 33 is rejected because the patentability of a product does not depend on the method used in producing the product.

Applicants respectfully traverse this rejection on the grounds that the Puricase® trademark registration satisfies neither the criteria for anticipation under 35 U.S.C. §102(b) nor the criteria for an enabling disclosure required for a prior art reference relied upon to make a statutory rejection.

To anticipate a claim under 35 U.S.C. §102(b), a reference must teach each and every element of the claim, such that the invention must be shown in as complete detail as is contained in the claim. MPEP § 2131. Here, Claims 2-8, 17-28, and 33 all depend directly or indirectly from Claim 1, which recites "[p]urified urate oxidase (uricase) substantially free of aggregates larger than octamers." The Puricase® trademark registration reference does not explicitly or inherently teach purified urate oxidase (uricase) substantially free of aggregates larger than

octamers and thus, does not anticipate Claim 1. The Puricase® trademark registration reference does not teach the additional claim limitations found in Claims 2-8, 17-28, and 33. Because the Puricase® trademark registration reference does not teach each and every element as set forth in the claims, this reference does not anticipate the rejected claims under 35 U.S.C. §1-2(b) and should be withdrawn.

Not only does the Puricase® trademark reference not anticipate the rejected claims, it is not even suitable as a prior art reference for purposes of statutory rejection. In order to make a *prima facie* case for rejection, a prior art reference must be operable, that is, it must contain an enabling disclosure such that "one of ordinary skill in the art could have combined the publication's description with his [or her] own knowledge to make the claimed invention describes the claimed invention" MPEP §2121.01, citing *In re Donohue*, 766 F.2d at 621. In the present case, the Office Action asserts that "[b]ecause the reference uricase is used as a therapeutic composition in humans, one skilled in the art would recognize that said uricase is free of large aggregates." First, Applicants point out that the Puricase® registration merely discloses a mark for use in "pharmaceutical preparations containing uricase coupled to polyethylene glycol for use in the treatment of hyperuricemia and related conditions" and does not itself teach a uricase substantially free of large aggregates. Second, one of skill in the art would, upon reading this trademark registration, not recognize that the uricase in the referenced pharmaceutical preparations is free of large aggregates. The Office Action has not provided any basis for asserting that it was known in the art that only uricase free of large aggregates would be used for pharmaceutical preparations as disclosed in the Puricase® trademark registration. Because the Puricase® trademark registration does not even constitute an enabling disclosure, this reference is not citable as prior art and rejections based on this reference should be withdrawn.

Regarding the rejection of Claim 33 on grounds that the patentability of a product does not depend on the method used in producing the product, Applicants point out that Claim 33 is directed to an isolated uricase prepared by the method of Claim 29, which separates uricase aggregates larger than octamers and excludes such aggregates from the purified uricase. The Puricase® trademark registration reference does not teach an isolated uricase substantially free of aggregates larger than octamers. Thus, the Puricase® trademark registration does not anticipate Claim 33 and this rejection should be withdrawn.

Rejections under 35 U.S.C. §103

Rejection of Claims 1, 4, and 9 over Puricase ® in view of Wu *et al.*(1989)

Claims 1,4, and 9 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Puricase® (Registration No. 2,246,623) trademark registration in view of Wu *et al.* (*Proc Natl Acad Sci USA* **86**:9412-9416 (1989)). According to the Office Action, Puricase® teaches a uricase, but not a uricase in which His at position 97 has replaced Tyr, and Wu *et al* (1989) teach that baboon, porcine, and mouse uricases are highly conserved. According to the Office Action, it would have been obvious "to make a uricase by replacing Tyr 97 of the baboon uricase with Try97 [sic] of the porcine uricase" and one would be motivated to make this replacement "because histidines play a role in binding copper and uricase is a copper binding enzyme." Applicants assume the Office Action intended to suggest replacing Tyr 97 of the baboon uricase with a histidine, and respectfully traverse.

The Patent Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP §2142 To establish a *prima facie* case of obviousness, the Office Action must provide some suggestion of the desirability of doing what the inventor has done, there must be a reasonable expectation of success, and the prior art references when combined must teach or suggest all of the claim limitations. MPEP §2142. Applicants respectfully submit that the Office Action has not established a *prima facie* case of obviousness because the references when combined do not teach the claimed invention. As the Office Action admits, Puricase® does not teach a uricase in which His at position 97 has replaced Tyr. Likewise, Wu *et al.* (1989) does not teach a modified uricase in which His at position 97 has replaced Tyr. As discussed above, the Puricase® trademark registration is not available as a prior art reference, and even if it were, the combination of a trademark registration and the Wu *et al.* (1989) reference does not teach or suggest the uricase in which His at position 97 has replaced Tyr, as in Claim 9. Finally, Applicants respectfully disagree that "[o]ne would be motivated to replace a residue with a conserved residue because conserved amino acids very often impart the characteristic property of an enzyme and because histidines play a role in binding copper and uricase is a copper binding enzyme." (Office Action, page 4) on the grounds that uricase is not a copper binding enzyme. Thus, the Examiner has not provided motivation to make a uricase in which His at position 97

has replaced Tyr. Because a *prima facie* case of obviousness has not been established, the rejection of Claims 1, 4, and 9 should be withdrawn.

Rejection of Claims 1, 4, and 10 over Puricase® in view of Wu *et al.* (1989)

Claims 1, 4, and 10 are rejected under 35 U.S.C. §103(a) as being unpatentable over Puricase® in view of Wu *et al.* (*Proc Natl Acad Sci USA* **86**:9412-9416 (1989)). According to the Office Action, Puricase® teaches a uricase, but does not teach a uricase truncated at one or both termini. According to the Office Action, the Wu *et al.* (1989) reference teaches that "porcine urate oxidase is six amino acid residues shorter than that of rat uricase (page 9414, 2nd column) but the two uricases are highly conserved throught the coding region (page 9413, 4th paragraph)." According to the Office Action, it would have been obvious "to make a functional uricase of a smaller size by deleting residues from both N-terminus." Applicants respectfully traverse.

The Patent Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP §2142 To establish a *prima facie* case of obviousness, the Office Action must provide some suggestion of the desirability of doing what the inventor has done, there must be a reasonable expectation of success, and the prior art references when combined must teach or suggest all the claim limitations. MPEP §2142. As discussed above, the Puricase® trademark registration is not available as prior art for statutory rejection, and even if it were, the combination of the Puricase® trademark registration and the Wu *et al.* (1989) reference do not teach a truncated uricase. The Wu *et al.* (1989) reference teaches that urate oxidase (uricase) isolated from porcine liver is six amino acid residues shorter than urate oxidase isolated from rat liver but the two uricases are highly conserved. Applicants wish to point out that the porcine sequence (SEQ ID NO: 1), has the same number of residues (304) as the baboon sequence (SEQ ID NO: 2), and the coding sequence of the porcine sequence is not truncated. Because neither the Puricase® trademark registration nor the Wu *et al.* (1989) reference teaches a truncated uricase, the references, alone or in combination, do not teach or suggest all the claim limitations. Thus, a *prima facie* case of obviousness has not been established and the rejection of Claims 1, 4, and 10 should be withdrawn.

Rejections under 35 U.S.C. §112

Claims 5, 9, and 10 are rejected under 35 U.S.C. §112, 2nd paragraph, as being indefinite. Claims 5 and 9 are rejected on the grounds that the metes and bounds of the claim are still unclear "because various polypeptides can be 'substantially' the sequence of a porcine, bovine, ovine, or baboon liver uricase and many polypeptides can contain a portion of porcine and baboon liver uricases." Office Action, page 7. Applicants respectfully traverse.

The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. §112. MPEP §2173.05(b) In the present case, the specification states that, "[w]hen the uricase is a recombinant form of any of the uricases mentioned herein, the recombinant form may have substantially the sequence of the naturally occurring form." (page 9, lines 14-16). The specification discloses the sequence of the naturally occurring form of porcine uricase (SEQ ID NO: 1) and the sequence of the naturally occurring form of baboon uricase (SEQ ID NO: 2). The specification teaches that the uricase may be bovine liver or ovine liver uricase (page 3, lines 30-31) and teaches a method for isolating uricase in Example 1 (page 15, lines 3-28). Determining the sequence of isolated uricase is routine for one of skill in the art. Thus, the specification teaches the sequence of, or methods to determine the sequence of, naturally occurring forms of uricase. Knowing the sequence of naturally occurring forms of uricase enables one of skill in the art to identify sequences that fall within the claim limitation "substantially the sequence" of porcine, bovine, ovine, or baboon liver uricase. Because the meaning of "substantially the sequence" is sufficiently definite in light of the disclosure in the specification, the rejection of Claims 5 and 9 under 35 U.S.C. §112, 2nd paragraph should be withdrawn.

Claim 10 is rejected as being indefinite, apparently for reciting that the claimed uricase comprises an amino terminus and a carboxy terminus, which the Office Action finds redundant. Applicants respectfully disagree. First, reciting the carboxy terminus and amino terminus provides definiteness and antecedent basis for the latter half of the claim, which recites truncation at one or both termini. Second, Applicants point out that branched polypeptides, hyperbranched polypeptides, or cyclic polypeptides are amino acid sequences that do not have an amino and carboxyl terminus. Branched and hyperbranched polypeptides have multiple termini, and cyclic polypeptides have no termini. Because recitation of an amino terminus and a carboxy terminus

of a uricase provides definiteness by particularly pointing out and distinctly claiming the subject matter which the Applicants regard as the invention, the rejection of Claim 10 under 35 U.S.C. §112 2nd paragraph should be withdrawn.

Claim Objections

Claim 10 is objected to under 37 C.F.R. §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 10 depends on Claim 4, which depends from Claim 1. Claim 1 is drawn to naturally occurring and recombinant uricases, and Claim 4, dependent from Claim 1, is drawn to recombinant uricases. Thus, Claim 10, drawn to truncated recombinant uricases does further limit the subject matter of Claim 1 and Claim 4 and objections to Claim 10 should be withdrawn.

Conclusion

In light of the foregoing Remarks, Applicants respectfully request that all outstanding claim rejections and objections be withdrawn and Claims 1-10, 17-28, and 33 be found in condition for allowance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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